The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Rilapladib (SB659032)

Study Number: LPZ114458

Title: Study LPZ114458, a phase 2a study to evaluate the effect of rilapladib (SB-659032) on biomarkers related to the pathogenesis and progression of Alzheimer's disease

Rationale: Risk factors for cerebrovascular pathology overlap with those of Alzheimer's disease (AD) with a number of studies suggesting that the combination of AD and vascular pathologies accelerates the onset and progression of dementia. The study was designed to explore whether rilapladib can produce pharmacodynamic effects on amyloid beta peptide (Aβ) that are consistent with a change in the transport of the peptide from the CNS.

Phase: 2a

Study Period: 04-Oct-2011 until 18-Feb-2013

Study Design: This was a randomised, double-blind, placebo controlled, parallel group, study to evaluate the effect of rilapladib on biomarkers related to the pathogenesis and progression of AD and cognitive function. Subjects took 250mg of rilapladib or placebo once daily for a period of 24 weeks in addition to their stable background therapy consisting of an acetylcholinesterase inhibitor (AChEI) and/or memantine. Total duration of participation for each subject was approximately 30 weeks comprising approximately 4 weeks screening, 24 weeks treatment period and 2 weeks follow-up.

Centres: This study was conducted at 24 centres in 6 countries: 10 sites Germany; 6 Spain; 5 Italy; 1 Sweden; 1 Bulgaria; 1 Canada.

Indication: Alzheimer's disease

Treatment: Subjects received 250 mg rilapladib or matching placebo once daily following breakfast for 24 weeks.

Objectives: The primary objective was to examine in an exploratory manner whether rilapladib produced changes in cerebrospinal fluid (CSF) biomarkers that were consistent with effects on increased central nervous system (CNS) Aβ clearance in Alzheimer's disease (AD) patients and whether these findings were associated with changes in CSF neurodegenerative markers and selected cognitive endpoints

Primary Outcome (Endpoints)/Efficacy :

- Change from baseline in CSF $A\beta_{42}$, $A\beta_{40}$ and $A\beta_{42}$/ $A\beta_{40}$ ratios at week 24.
- Change from baseline in CSF tau and P-tau measures at week 24.
- Change from baseline in the CogState battery working memory/executive function composite score at week 24.

Secondary Outcome (Endpoints)/Efficacy :

- Change from baseline in CSF albumin quotient at week 24.
- Change from baseline in plasma levels of $A\beta_{42}$, $A\beta_{40}$ and ratio $A\beta_{42}/A\beta_{40}$ at week 24.
- Change from baseline in plasma Lp-PLA_2 activity at week 24.
- Change from baseline in CogState battery overall composite score.
- Change from baseline in CogState battery attention composite score.

Statistical Methods:

Assuming a post randomisation drop-out rate of 15%, approximately 120 subjects were randomised in order to ensure a total of 102 evaluable subjects (51 per group). A sample size of 51 evaluable subjects per arm allowed a difference of 70pg/ml in CSF $A\beta_{42}$ between placebo and rilapladib to be detected with 80% power at a 5% (2-sided) significance level assuming an

underlying SD of 120.

Three populations were defined for efficacy and safety analyses: Safety (subjects randomised who took at least one dose of study medication), Intent-to treat (ITT) (subjects in the Safety population who also had at least one post-baseline efficacy assessment), and Per Protocol (PP) (subjects in the ITT population who were not major protocol deviators).

Change from baseline in CSF parameters were analysed using an analysis of covariance (ANCOVA), adjusting for baseline CSF parameter, age and treatment. Change from baseline in plasma biomarker parameters and CogState endpoints were analysed using a mixed model for repeated measures (MMRM), assuming an unstructured covariance matrix, with the following terms included in the model treatment, visit, baseline, treatment by visit and baseline by visit.

Primary inference was based on the End of Study/Week 24 treatment differences between placebo and rilapladib 250mg for the ITT population for CSF Aβ1-42 and CogState EF/WM respectively. Statistical significance was interpreted using a 2-sided test at the 5% significance level for these primary comparisons of interest only. CSF Aβ1-42 and CogState EF/WM were also analysed using the PP population.

Results for the analysis of the cognitive endpoints are presented as differences in standardised scores (Z-scores, using the mean and standard deviation (SD) for the ITT population at baseline).

Safety data were summarised using descriptive statistics.

Study Population:

The planned study population was subjects with a diagnosis of possible AD with radiological evidence of cerebrovascular disease.

Key Inclusion Criteria

1. A clinical diagnosis of possible Alzheimer's disease in accordance with the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, with radiological (Magnetic Resonance Imaging [MRI] or Computed Tomography [CT]) evidence of significant cerebrovascular disease (CVD), assessed within the last 12 months
2. Male or female between 50 and 80 years of age inclusive, at the time of signing the informed consent.
3. Subject has a documented history of at least 6 months of ongoing Alzheimer's disease therapy (AChEIs and/or memantine) with stable dosing for at least the last 2 months (and with no intent to change for the duration of the study).
4. Mini-Mental Status Examination (MMSE) score between 20 and 26 at Screening.
5. Clinical Dementia Rating Scale (CDR) score of 0.5 or 1.0 at Screening.
6. A female subject is eligible to participate if she is of non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea; or of child-bearing potential and agrees to use acceptable contraception methods
7. Subject has provided full written informed consent prior to the performance of any protocol-specified procedure; or if the subject is unable to provide informed consent due to cognitive status, the subject will provide assent and full written informed consent will be provided by a legally acceptable representative
8. The subject has a dedicated caregiver who is willing to supervise participation in the study
9. In the opinion of the investigator, the subject has the ability to comply with study procedures (cognitive and other testing) and is fluent in the language used for the administration of the cognitive tests.

Key Exclusion Criteria

1. History and/or evidence of any other CNS disorder that could be interpreted as a cause of dementia: e.g. structural or developmental abnormality, epilepsy, infectious, degenerative or inflammatory/demyelinating CNS conditions such as, Parkinson's disease and frontotemporal dementia
2. History of significant psychiatric illness such as schizophrenia or bipolar affective disorder that in the opinion of the Investigator would interfere with participation in the study; major depressive disorder (according to DSM-IV) in the past year; current active depression requiring initiation of treatment (or is believed to account for substantial degree of cognitive impairment)
3. Evidence of the following disorders: current vitamin B12 deficiency, positive syphilis serology (unless neurosyphilis was ruled out) or active thyroid dysfunction (particularly suggestive of hypothyroidism), including abnormally high or low serum levels of thyroid stimulating hormone (TSH), where this is thought to be the cause of, or to contribute to the severity of the subject's dementia.
4. History of alcohol or other substance abuse, according to the DSM-IV criteria, or recent or remote history of the same if that could be a contributing factor to dementia.
5. History of intra cerebral haemorrhage due to any of the following causes: cerebral amyloid angiopathy, uncontrolled hypertension, cerebral arteriovenous malformation, coagulopathy, CNS vasculitis or any other condition that the investigator and/or medical monitor considers as a relevant risk factor for intracerebral haemorrhage
6. Recent (i.e.,<6 months from Screening Visit) cardiovascular event defined as:
    a. ST-elevation MI or non-ST-elevation MI, confirmed by cardiac enzyme elevation and ECG changes
    b. coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft)
    c. stroke of any etiology
    d. resuscitated sudden death
    e. prior carotid surgery or stenting procedure
7. Poorly controlled hypertension despite lifestyle modifications and pharmacotherapy (either systolic blood pressure >160mmHg or diastolic blood pressure >110mmHg)
8. QTcB interval >450 msec; or QTcB > 480 msec in subjects with bundle branch block based on ECG assessment at the Screening visit.
9. HbA1c >12.0 at Screening, or uncontrolled diabetes in the opinion of the investigator.
10. History of glaucoma or any other findings in the baseline eye exam that, in the opinion of the investigator, would exclude the subject from participation in the study.
11. History of adult asthma (or reactive airway disease) manifested by bronchospasm in the past 6 months, or currently taking regular anti-asthmatic medication(s).
12. Previous history of anaphylaxis, severe allergic reaction or history of hypersensitivity to any of the components of the formulation.
13. Significant abnormalities on clinical chemistry, haematology or urinalysis at Screening, including clinically significant anaemia.
14. History of chronic viral hepatitis (including presence of B surface antigen or hepatitis C antibody), or other chronic hepatic disorders.
15. Abnormal Screening blood tests exceeding any of the limits defined below:
    a. Alanine transaminase (ALT) or aspartate transaminase (AST) >1.5 x the upper limit of normal (ULN)
    b. Alkaline phosphatase (AP) and bilirubin >1.5X ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
    c. Calculated creatinine clearance < 30 ml/min (per Cockcroft & Gault) at Screening
16. Other clinically significant abnormality on physical (including neurological), laboratory or ECG examination that could be detrimental to the subject in the opinion of the Investigator or

could compromise the integrity of the study.

17. Planned major surgery within the study period.
18. Use of systemic steroids or other immunosuppressants within the last 30 days prior to screening.
19. Current treatment with barbiturates, MAO inhibitors, butyrophenones, phenothiazines and other "conventional" antipsychotic within 30 days or 5 half-lives prior to Screening, whichever is longer.
20. Treatment with antidepressants, (other than MAO inhibitors), thyroid hormones, atypical antipsychotics (e.g. risperidone), benzodiazepines and other sedatives / hypnotics unless prescribed at a stable dose for at least 2 months prior to Screening. Note: Benzodiazepines or other sedatives/hypnotics (including antihistamines) with half-life less than 6 hours can be taken on a prn (as needed) basis but must not be taken within 5 half lives prior to cognitive testing.
21. Current treatment with known potent inhibitors of CYP3A4 (e.g. ketoconazole, rifampin, modafinil).
22. Current treatment with known potent Pgp inhibitors (itraconazole, ketoconazole, cyclosporin, loperamide, diltiazem, verapamil, spironolactone, quinidine, bepridil, quinine, carvedilol)
23. Cognitive tasks prescribed for cognitive rehabilitation and performed under medical supervision in the 6 months prior to screening and/or during study
24. Investigational medications or devices including symptomatic AD treatment during the 60 days prior to the Screening visit, or within 5 half-lives of use of the investigational drug prior to the Screening Visit, whichever is longer.
25. Participation in another investigational drug (with the exception of anti-amyloid monoclonal antibodies [mAbs]) or device study where subject was treated chronically (i.e. > 1 single dose) with a study agent intended to impact AD progression during the 12 months prior to the Screening visit.
    a. Subjects who participated in an investigational drug study that involved chronic dosing with a monoclonal antibody at any time in the past are excluded from this study, unless it is known that they received placebo during the previous study.
    b. Subjects who participated in previous single-dose studies of anti-amyloid mAbs will be permitted provided the subject's dose of the mAb is at least 5 half-lives removed; the subjects did not experience any moderate adverse events classified as possibly drug-related or any serious adverse event during that study; the subject did not drop out of the previous study (i.e. completed all safety assessments)
26. Subjects, who in the investigator's judgement, pose a significant suicide risk (e.g. history of suicidal behaviour in the last 6 months and/or any suicidal ideation of type 4 or 5 on the C-SSRS in the last 2 months).
27. Subject or caregiver is an immediate family member or employee of the participating Investigator, any of the participating site staff or GSK staff.
28. Any contraindication to lumbar puncture or insertion of CSF catheter, including but not limited to
    a. Thrombocytopenia or other coagulation disorders (including subjects receiving coumarin-derived anti-coagulants or low-molecular-weight heparin).
    b. The presence of cutaneous or soft tissue infection overlying or adjacent to the site of lumbar puncture.
    c. Previous spinal surgery that could complicate access to the subarachnoid space.
    d. Suspicion of increased intracranial pressure due to a cerebral mass.

	Placebo	**Rilapladib**
Number of Subjects:		
Planned, N	60	60
Randomised, N	62	62
Safety	62	61

ITT	61	60
PP	54	50
Completed, n (% of Safety Population)	56 (90%)	52 (85%)
Total Number Subjects Withdrawn, n (%of Safety Population)	6 (10%)	9 (15%)
Withdrawn due to Adverse Events n (%of Safety Population)	2 (3%)	7 (11%)
Withdrawn due to Lack of Efficacy n (%of Safety Population)	0 (0%)	0 (0%)
Withdrawn due to Protocol Deviation	1 (2%)	0
Lost to follow-up	0	1 (2%)
Withdrew consent	3 (5%)	1 (2%)
Demographics	**Placebo**	**Rilapladib**
N (ITT)	61	60
Females: Males	28 (46%):33 (54%)	32 (53%):28 (47%)
Mean Age, years (SD)	73.1 (5.40)	72.9 (5.15)
White, n (%)	61 (100%)	60 (100%)
MMSE, mean (SD)	22.9 (1.98)	22.8 (2.12)
Primary Efficacy Results at Week 24: (ITT Population)		
CSF Abeta1-42 (ng/L)	**Placebo**	**Rilapladib**
Adjusted Mean Change from Baseline (SE)	-6.3 (18.10)	33.6 (19.02)
Difference between treatments	39.8	
95% Confidence Interval	-12.4, 92.0	
p-value	0.133	
CogState Working Memory/Executive Function Composite Score	**Placebo**	**Rilapladib**
Adjusted Mean Change from Baseline in Z-score (SE)	-0.150 (0.0501)	0.016 (0.0538)
Difference between treatments	0.167	
95% Confidence Interval	0.021, 0.313	
p-value	0.026	
CSF Abeta1-40 (ng/L)	**Placebo**	**Rilapladib**
Adjusted Mean Change from Baseline (SE)	-77.4 (181.33)	-327.7 (190.56)
Difference between treatments	-250.3	
95% Confidence Interval	-772.9, 272.2	
CSF Abeta1-42/Abeta1-40 Ratio	**Placebo**	**Rilapladib**
Adjusted Mean Change from Baseline (SE)	0.002 (0.0068)	0.018 (0.0071)
Difference between treatments	0.016	
95% Confidence Interval	-0.003, 0.036	
CSF t-tau (ng/L)	**Placebo**	**Rilapladib**
Adjusted Mean Change from Baseline (SE)	38.2 (29.98)	-18.8 (31.90)
Difference between treatments	-57.1	
95% Confidence Interval	-144.5, 30.3	
CSF 181P-tau (ng/L)	**Placebo**	**Rilapladib**
Adjusted Mean Change from Baseline (SE)	1.3 (1.67)	-1.7 (1.76)
Difference between treatments	-3.0	
95% Confidence Interval	-7.9, 1.8	
Secondary Outcome Results at Week 24 (ITT Population)		
CSF Albumin Quotient	**Placebo**	**Rilapladib**
Difference between treatments	-0.24	
95% Confidence Interval	-0.74, 0.26	
Plasma Abeta1-42 (ng/L)	**Placebo**	**Rilapladib**
Difference between treatments	-1.3	
95% Confidence Interval	-3.9, 1.2	
Plasma Abeta1-40 (ng/L)	**Placebo**	**Rilapladib**
Difference between treatments	1.0	
95% Confidence Interval	-10.2, 12.2	
Plasma Abeta 1-42/Abeta1-40 Ratio	**Placebo**	**Rilapladib**
Difference between treatments	-0.003	
95% Confidence Interval	-0.016, 0.010	

Plasma LpPLA2 Activity (% Inhibition)	**Placebo**	**Rilapladib**
n	53	47
% Inhibition at Week 24 (SD)	-3.86 (30.228)	83.59 (10.483)
CogState Overall Composite Score	**Placebo**	**Rilapladib**
Difference between treatments	0.138	
95% Confidence Interval	0.010, 0.267	
CogState Attention Composite Score	**Placebo**	**Rilapladib**
n	55	48
Mean Change from Baseline in Z-score (SD)	-0.112 (0.4685)	0.030 (0.6178)

Safety Results: AEs were collected from the start of Study Treatment until the follow-up contact. SAEs were collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication was recorded from the time a subject consents to participate in the study up to and including any follow-up contact. An on therapy adverse event (AE/SAE) was defined as an AE/SAE with onset on or after the start date of study medication but not later than ten days after the last date of study medicationAEs presented in the table below are on-therapy AEs

	Placebo	**Rilapladib**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	39 (63)	39 (64)
Headache	10 (16)	3 (5)
Dizziness	4 (6)	3 (5)
Nausea	5 (8)	2 (3)
Urinary tract infection	6 (10)	1 (2)
Diarrhoea	2 (3)	4 (7)
Cystitis	0	4 (7)
Fatigue	3 (5)	2 (3)
Hypertension	2 (3)	2 (3)
Syncope	0	2 (3)
Nasopharyngitis	1 (2)	2 (3)
Pneumonia	2 (3)	0
Vomiting	2 (3)	1 (2)
Agitation	1 (2)	2 (3)
Fall	1 (2)	2 (3)

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

	Placebo	**Rilapladib**
Subjects with non-fatal SAEs on therapy, n (%)	5 (8)	8 (13)
	n (%) [related]	**n (%) [related]**

Fall	0	1 (2) [0]
Femoral neck fracture	0	1 (2) [0]
Fractured coccyx	1 (2) [0]	0
Scapula fracture	0	1 (2) [0]
Sternal fracture	1 (2) [0]	0
Colitis microscopic	0	1 (2) [0]
Inguinal hernia	1 (2) [0]	0
Large intestine perforation	1 (2) [0]	0
Cerebral haemorrhage	0	1 (2) [0]
Complex partial seizures	0	1 (2) [0]
Dizziness	0	1 (2) [0]
Upper respiratory tract infection	1 (2) [0]	0
Vestibular neuronitis	1 (2) [0]	0
Bradycardia	0	1 (2) [0]
Subjects with non-fatal SAEs during follow-up, n (%)	1 (2)	1 (2)
Pneumonia	1 (2) [0]	0
Leukaemia	0	1 (2) [0]
Subjects with fatal SAEs on therapy, n (%)	**n (%) [related]**	**n (%) [related]**
Cerebral haemorrhage	0	1 (2) [1]
Subjects with fatal SAEs during follow-up, n (%)	**n (%) [related]**	**n (%) [related]**
Pulmonary embolism	1 (2) [0]	0

Conclusion:

The difference between rilapladib and placebo for CSF Aβ 1-42 at Week 24 was not statistically significant. The change from baseline in working memory/executive function at 24 weeks was statistically significant.

The change from baseline for the overall composite cognitive score was similar to that for working memory/executive function. CSF Abeta1-40 showed decreases from baseline for both treatments. The ratio of CSF Abeta1-42/Abeta1-40 showed little change with either treatment. CSF t-tau, p-tau and albumin quotient increased from baseline with placebo and decreased with rilapladib. Plasma Abeta1-42, Abeta1-40 and the ratio of Abeta1-42/Abeta1-40 showed little change for either treatment. Plasma LpPLA2 activity was inhibited by approximately 80% by rilapladib and showed little change with placebo.

Adverse events were experienced by 39 subjects in each treatment group. The most common AEs in the placebo group were headache, urinary tract infection, nausea and dizziness. The most common AEs in the rilapladib group were diarrhoea, cystitis, headache and dizziness. Non-fatal SAEs were reported for 5 subjects in the placebo group and 8 subjects in the rilapladib group. No individual SAE was reported by more than one subject. AEs leading to premature discontinuation from the study were reported for 2 subjects in the placebo group and 7 subjects in the rilapladib group. One fatal SAE was reported in each group (cerebral haemorrhage and pulmonary embolism in the rilapladib and placebo group, respectively).